

**UNITED STATES DEPARTMENT OF COMMERCE****Patent and Trademark Office**

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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09/115,963 07/15/98 SCHNEIDER

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EXAMINER

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ART UNIT	PAPER NUMBER
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1619

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DATE MAILED: 08/29/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)
	09/115,963	SCHNEIDER ET AL.
	Examiner	Art Unit
	Gary E Hollinden, Ph.D.	1619

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
 If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
 If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
 Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

1) Responsive to communication(s) filed on 3/29/00, 4/14/00, 5/22/00.
 2a) This action is **FINAL**. 2b) This action is non-final.
 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4) Claim(s) 1-7 and 13-48 is/are pending in the application.
 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
 5) Claim(s) _____ is/are allowed.
 6) Claim(s) 1-7, 13-48 is/are rejected.
 7) Claim(s) _____ is/are objected to.
 8) Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) The specification is objected to by the Examiner.
 10) The drawing(s) filed on _____ is/are objected to by the Examiner.
 11) The proposed drawing correction filed on _____ is: a) approved b) disapproved.
 12) The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).
 a) All b) Some * c) None of the CERTIFIED copies of the priority documents have been:
 1. received.
 2. received in Application No. (Series Code / Serial Number) _____.
 3. received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
 * See the attached detailed Office action for a list of the certified copies not received.
 14) Acknowledgement is made of a claim for domestic priority under 35 U.S.C. & 119(e).

Attachment(s)

15) <input type="checkbox"/> Notice of References Cited (PTO-892)	18) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). _____
16) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)	19) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)
17) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____	20) <input type="checkbox"/> Other: _____

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This Office Action is a response to the amendment filed on March 29, 2000 wherein claims 1, 2, 13, 15-20, and 32-34 were amended. Currently, Claims 1-7 and 13-18 are pending in this application and will be examined on their merits.

Administrative Notice

In the response filed on March 29, 2000, Patentee contests Examiner's Administrative Notice that various terms of art¹ have been used so interchangeably in the art that no clear distinction can be made between them solely on the basis of the term used. In support of their contention, Patentee asserts that Schneider et al. indicate a distinction between microbubbles, which are taught as not having a material boundary or envelope, and microballoons which do have a material envelope. Patentee's arguments have been fully considered but are not considered persuasive for the following reasons:

1) While the term "microbubble" appears to be consistent throughout their patent, other references exist which clearly define the term differently:

a) Feinstein² clearly teaches a much broader interpretation of the term:

The prior art contrast agents were liquids containing microbubbles of gas, which sometimes were encapsulated with gelatin or saccharine and sometimes were produced by mechanically agitating, i.e. hand-shaking, mixtures of various liquids.

Thus, Feinstein's use of the term includes compositions wherein the gas bubbles are enclosed by a material envelope.

b) Quay³ also defines the term microbubbles as including compositions wherein the gas bubble is surrounded by a material envelope as reproduced below:

Composite substances such as gelatin encapsulated microbubbles, gas-incorporated liposomes, sonicated partially denatured proteins and emulsions containing highly fluorinated organic compounds have also been studied in an attempt to develop an agent that has certain ideal qualities, primarily, stability in the body and the ability to provide significantly enhanced contrast in an ultrasound image.

¹e.g. microbubbles, microspheres, microcapsules, microballoons, free gas bubbles, liposomes, etc.

²US Patent 4,572,203; issued February 25, 1996; cited portion is from column 2, lines 14-18

³US Patent 5,558,854; issued September 24, 1996; cited portion is from column 1, line 67 - column 2 line 7.

2) Similarly, while Schneider et al. indicated that the term microballoon would necessarily be composed of a gas bubble surrounded by a material envelope, other artisans in this field do not make the same distinction. For example Klaveness et al.⁴ teach:

Any biocompatible gas may be employed in the contrast agents of the invention, for example air, nitrogen, oxygen, hydrogen, nitrous oxide, carbon dioxide, helium, argon, sulfur hexafluoride and low molecular weight optionally fluorinated hydrocarbons such as methane, acetylene or carbon tetrafluoride. The gas may be free within the microbubble, advantageously in the form of a gas-filled "microballoon" since the echogenicity of such products may be enhanced by virtue of their relatively flexible nature. Alternatively the gas may be trapped or entrained within a containing substance.

3) In addition, Schneider et al.⁵ teaches that the term "microsphere" would encompass both microbubbles and microballoons as indicated in the passage reproduced below:

It is well known that microbubbles like microspheres or micro globules of air or a gas, e.g. microbubbles or microballoons, suspended in a liquid are exceptionally efficient ultrasound reflectors for echography.

Since Schneider et al. make a distinction between microbubbles and microballoons later in their specification (as noted in Patentee's response), it is clear that their working definition of the term microsphere would include small gas bubbles which both do and do not have a material boundary or envelope.

Thus, it is apparent that most of the terms used to designate very small gas bubbles in an ultrasonic composition have not acquired a clear consistent definition. Instead, the terms are often used interchangeably and one must look to the context of the patent/ article to determine just what the term means in that particular reference. As stated by In re Zletz:⁶

"Mode of claim interpretation used by courts in litigation when interpreting claims of issued patents in connection with infringement or validity determinations is not mode of claim interpretation applicable during prosecution of pending application; rather, during patent examination claims must be interpreted as broadly as they reasonably allow, in order to achieve complete exploration of applicant's invention and its relationship to prior art, so that ambiguities can be recognized, scope and breadth of language explored, and clarification imposed."

⁴US Patent 5,536,490; issued July 16, 1996. Portion cited is from column 2, lines 34-39

⁵US Patent 5,271,928; issued December 21, 1993. Portion cited is from column 1, lines 21-24.

⁶13 USPQ 2d 1320, CA FC 1989

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*In re Morris*⁷ expands on this principle:

"PTO is not required, in course of prosecution, to interpret claim in patent applications ~~in same manner as courts interpret claims during infringement suits; instead, PTO applies to language of proposed claims broadest reasonable meaning of words in their ordinary usage as they would be understood by one of ordinary skill in art, taking into account whatever enlightenment by way of definitions or otherwise that may be afforded by written description in Applicant's specification.~~" [emphasis added]

Thus, the courts have urged the PTO to use a different standard in *ex parte* prosecution than that which is used in patent litigation. As shown by the example patents set forth above, those of ordinary skill in this art have applied very general and very overlapping meanings to most terms of art denoting gas filled spheres. Thus, the broadest reasonable interpretation which could be applied would be that most terms of art would encompass any bubble of gas that either has some type of shell/membrane/material layer of compound(s) at the interface between the gas and the surrounding liquid or not. Accordingly, while Applicant may be his/her own lexicographer, the Patent Office has been instructed by the courts to read claims in light of what one of ordinary skill in art would understand.

Consequently, the Administrative Notice stands that one must look to the actual materials included in a composition and the process of making it used to determine what it teaches, rather than relying on the particular term of art used to denote the bubble mixture.

Effective Priority Date

In the response filed on March 29, 2000,⁸ Patente asserts that the effective priority date of the instant claims should be that of the priority documents now claimed.⁹ Patente asserts that the particular species now claimed are inherently

⁷44 USPQ 2d 1023, CA FC 1997.

⁸In addition, to this response, the protest by DuPont, filed April 14, 2000, also addressed the effective priority date of the instant claims, as did Patente's response to the protest, filed May 22, 2000. Most of the discussion herein is directed to Patente's response. For those arguments made in the protest by Dupont which are sufficiently similar to the discussion contained herein, they will not be further discussed. However, the arguments made in the response to the protest which were actually made to the similar arguments in the protest will be discussed as they pertain to the arguments made herein.

⁹the two earliest documents being EP 90810262, filed April 2, 1990 and EP 90810367, filed May 18, 1990

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claimed as being part of the group of species encompassed by the term "Freon®".¹⁰ Patentee has also brought forward several declarants who each substantially assert that the artisan in this field would recognize the particular species now claimed are inherently part of the genus embraced by Freon®. Interestingly, Patentee also asserts that SF₆ which could not, by any stretch of the imagination, be considered a Freon® gas, should still be accorded priority because it is a fluorinated gas with similar properties and the two priority specifications allow for gases "like" the gases specifically named.

When claiming priority to an earlier application, the courts have held that (among other requirements) the claims of the instant application must have written description in the specification of the priority document. *Tronzo v. Biomet* provides an excellent synopsis:¹¹

"For a claim in a later filed application to be entitled to the filing date of an earlier application under 35 USC § 120, the earlier application must comply the written description requirement of 35 USC § 112 ¶ 1. § 112 ¶ 1 requires that the specification 'contain a written description of the invention, and of the manner and process of making and using it...' To meet this requirement, the disclosure of the earlier application, the parent, must reasonably convey to one of skill in the art that the inventor possessed the later-claimed subject matter at the time the parent application was filed. A disclosure in a parent application that merely renders the claimed invention obvious is not sufficient to meet the written description requirement, the disclosure must describe the claimed invention with all its limitations." [cites omitted]

In the instant case, Patentee is effectively asserting that the genus Freon® reasonably conveys to the artisan that the inventor originally possessed the eleven species now claimed¹² when they possessed the genus Freon® as a whole. *In re Ruschig*¹³ sets forth the proper test of description of a species within a genus:

"Disclosure such as that found in formula and words of claim does not amount to a disclosure, sufficient to support a specific claim, of every compound a skilled chemist can see is within scope of that claim; specific claims to single compounds require reasonably specific supporting disclosure; while naming is not essential, something more than disclosure of a class of 1000, 100, or even 48 compounds is required; given time, a chemist could name all of the half million compounds within scope of broadest claim,

¹⁰For purposes of this discussion, Examiner is using the definition of Freon® set forth by DuPont in their protest (reproduced below) since it appears that Patentee has also adopted this definition as well.

¹¹47 USPQ 2d 1829, CA FC 1998.

¹² as well as SF₆, purportedly similar to a Freon®.

¹³154 USPQ 118, CCPA 1967.

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which claim is supported by broad disclosure; this does not constitute support for each compound individually when separately claimed."

In the instant case, the term Freon® is defined by the owner of the trademark as:

"organic compounds containing one or more carbon atoms and fluorine. Chlorine, bromine, and hydrogen atoms also may be present."¹⁴

Thus, the genus embraced by the term Freon® would actually greatly exceed the standard used in *Ruschig*, since this definition of Freon® would include many thousands of compounds. Thus the bare disclosure of the genus clearly does not convey the instant species claimed.

Ruschig also states:

"It is an old custom in the woods to mark trails by making blaze marks on the trees. It is no help in finding a trail ... to be confronted simply by a large number of unmarked trees. Appellants are pointing to trees. We are looking for blaze marks which single out particular trees. We see none."

and further elucidated in *Fujikawa v. Wattanasin*:¹⁵

"In finding that Wattanasin's disclosure failed to sufficiently describe the proposed sub-genus, the Board again recognized that the compounds of the preferred count were not Wattanasin's preferred, and that his application contained no blazemarks as to what compound, other than those disclosed as preferred, might be of special interest. In the absence of such blazemarks, simply describing a large genus of compounds is not sufficient to satisfy the written description requirement as to particular species or sub-genuses."

Thus, the courts have further held that to get from the genus to particular species there must be some teaching pointing to those species. Patentees' priority documents are completely silent as to what property or properties (i.e. blaze marks) the Freon® gas should have in order to be a desired species. Indeed, there does not appear to be any properties which would particularly point to the instant species and exclude all of the other thousands of Freons®. Consequently, Patentee has a number of trees but no blaze marks which would signal the original intent of conveying the instant species. As for SF₆, Patentee is invited to provide competent case law which states that Patentee would be entitled to species that are actually outside of the original genus claimed.

¹⁴E.I. duPont de Nemours and CO. Technical Bulletin G-1 pages 1-10 (1987)

¹⁵39 USPQ 2d 1895, CA FC 1996

Patentee has brought forward several declarants which, each in their own way, state that the instant gases would be understood to be within the genus Freon®. Their statements regarding priority have been fully considered but are not deemed persuasive. Most importantly, the declarations are not on point since the test (as discussed above) is not whether, in hindsight, a particular species could be considered to be a part of the genus but instead is whether the disclosure itself points to the particular species now claimed.

In Patentee's response to the protest filed May 22, 2000, Patentee makes two assertions. First, Patentee asserts that case law does support that the disclosure of a genus is adequate written description for all the species contained therein. Second, Patentee asserts that there are sufficient blazemarks within the context of a Ruschig analysis to convey the instant species. These will be taken in turn:

1) Examiner concurs that an *ipsis verbis* disclosure is not necessary to satisfy the written description requirement; however, the courts have clearly held (as set forth hereinabove) that the disclosure of a genus alone, without some basis in the disclosure itself, for pointing to particular species, does not suffice. Turning to the case law cited:

a) *Union Oil v. Atlantic Richfield*¹⁶ is not on point because the case was not dealing with a genus-species relationship as is the present case. Further, in *Union Oil*, the specification thoroughly discussed the claimed compositions and their ranges of properties. The only omission was the exact chemical compounds which corresponded to the disclosed properties which was well known to artisans in that field at the time of the original invention.

b) *In re Driscoll*¹⁷ is not on point because the written description rejection hinged on whether a named class of substituents would represent a valid stand-alone sub-genus rather than the naming of particular species from a (broad) genus as is the case in the instant reissue. In fact, the CCPA

¹⁶54 USPQ 2d 1227, CA FC 2000.

¹⁷195 USPQ 434, CCPA 1977

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differentiated this case over *Ruschig* for that reason (see page 438). *In re Herschler*¹⁸ was also drawn to this fact pattern.

c) *University of California v. Eli Lilly*¹⁹ is not on point because it is drawn to sufficiency of written description for genetic material. The introductory statement cited by Patentee was simply dictum not relevant to the case.

Thus, none of the cited case law provided by Patentee sets forth a legal basis for interpreting the genus-species relationship in written description in a manner other than that set forth in *Ruschig*, which has been discussed in detail above.

2) Patentee asserts that there are three properties set forth in the priority disclosures (i.e. blazemarks) which would convey to the artisan the claimed species.

a) The first blazemark is that not all Freons® are gases at 25° C and 760 mmHg.²⁰ While this statement is true, many thousands of Freons® are gases at these conditions. Certainly, this blazemark does not differentiate the claimed gases from the many thousands of species which also possess this property.

b) The second blazemark is that since the non-Freon® gases are all very low molecular weight, this would point the artisan towards low molecular weight Freons®. This property is something of a stretch since it is an inference from the four other gases set forth rather than being an explicitly stated property. Insofar as it goes, it is true that the four other gases are all of very low molecular weight, the two largest being CO₂ at 46 and N₂O at 44. However, this point is not well taken because the instant claimed

¹⁸200 USPQ 711, CCPA 1979.

¹⁹43 USPQ 2d, CA FC 1997

²⁰Patentee parenthetically states that Freons® of greater than four carbons are not gases at 25° C and 760 mmHg. This statement is incorrect. Certain five, six, and (perhaps) even 7 carbon atom fluorochemicals are gases at 25° C and 760 mmHg depending upon degree of saturation, substitution and branching.

gases are not the lowest molecular weight Freons®. The lowest molecular weight Freon® would be 1-fluoro methane which is not claimed. Actually, dozens of Freons® have a lower molecular weight than the smallest Freon claimed!²¹ In addition, the instant species claimed encompass a large range of molecular weights: from perfluoromethane at 88 to CBrClF₂ at 165 to perfluorobutane at 238. Thus, a blazemark that the Freon® should have a low molecular weight would actually point to an entirely different group of compounds and would thus be more of a teaching away from Patentee's claimed species rather than towards them.

c) Patentee asserts that the requirement that the gas must be physiologically acceptable points to the claimed gases. However: i) All Freons® are fairly toxic at sufficiently high doses. ii) the dose of Freon® gas required to provide a good image for ultrasonic imaging is so minuscule that very few Freons® would be toxic. Thus, the number of Freons® which would be physiologically acceptable runs to the many thousands. iii) Patentee has not brought forward any evidence to prove that the claimed species are the most physiologically acceptable and indeed, it is unlikely that they are given that some of the species contain bromine and chlorine. Fourth, even if the claimed species were the most physiologically acceptable, the priority specification would not point to them because it does not state the most physiologically acceptable must be used. Rather it merely requires that they be physiologically acceptable and thus this blazemark again points to many thousands of Freons®.

Consequently, the blazemarks discussed by Patentee no more point to the particular species now claimed than a compass positioned in New York City would specifically point at 10 particular Inuit Indians in Canada. The priority disclosures simply do not convey to the artisan that Patentee was intending to possess the particular species now claimed.

²¹perfluoromethane has a molecular weight of 88.

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In the protest filed on April 14, 2000, the protestor, E.I. DuPont [Protestor], made a number of arguments concerning the proper effective filing date for the instant claims; many of which are similar to the arguments made herein. However, two arguments, not discussed above, deserve special mention:

1) Protestor asserts that since Patentee did not identify Freon® as a trademark, one of ordinary skill would not have been able to match up the term presented by Patentee with the generic definition by Dupont concerning Freons®. Such an argument appears specious on its face since the artisan merely has to look up the definition of the term in a chemical text or even a dictionary to determine both its meaning and that it is a trademark. Webster's Ninth New Collegiate dictionary defines it as follows:

Fre-on [pronunciation omitted] trademark - used for any of various nonflammable gaseous and liquid fluorocarbons used as refrigerants and as propellants for aerosols.

Certainly, a scientist or physician with advanced degrees, when confronted with a term they are not familiar with, would avail themselves of various texts, including a dictionary, so as determine the meaning of the term. It is important to note that the word "freon" has no meaning that is contrary to that given above.

2) Protestor's discussion of the file wrapper estoppel created during the original prosecution of the instant patent is clearly on point and is adopted by the Examiner herein. In short, the arguments set forth in the original prosecution of the instant patent regarding obviousness create a file wrapper estoppel against asserting written description of the instant invention to the now claimed priority documents. As set forth in *Tronzo v. Biomet*:²²

"...A disclosure in a parent application that merely renders the claimed invention obvious is not sufficient to meet the written description requirement, the disclosure must describe the claimed invention with all its limitations."

Thus, the CA FC has held that the written description standard is a higher standard than whether the priority document's disclosure could render the instant claims obvious. Therefore, Patentee's admissions in the original prosecution that the priority disclosures provide at best a shotgun disclosure

²² 47 USPQ 2d 1829, CA FC 1998; see also *Lockwood v. American Airlines*, 41 USPQ 2d 1961

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and fail to even render the prosecuted claims obvious estop Patentee from now claiming priority to those documents.

It is noted that Applicants response to the protest, filed May 22, 2000, Patentee did not discuss either of the issues discussed above.

For all the reasons set forth above, the effective filing date of the instant claims will still be considered to be the filing date of the § 119 European priority document originally claimed in this Patent i.e. EP 92810046, filed January 23, 1992.

§ 102 Rejection

The Applicant's response in the amendment filed on March 29, 2000²³ to the rejection made by the Examiner under 35 U.S.C. § 102 fully meet the deficiencies encompassed by said rejection. Therefore, said rejection is hereby withdrawn. As will be discussed in the obviousness rejection below, Albayrak et al. does teach all the elements of the claim designated invention; however, Albayrak et al. fail to teach all the elements together as set forth in the claim.²⁴

§ 103 Rejection

The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Subject matter developed by another person, which qualifies as prior art only under subsection (f) and (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the

²³and further amplified in the response to protest filed on May 22, 2000.

²⁴see *Richardson v. Suzuki Motor*, 9 USPQ 2d 1913, CA FC 1989.

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invention was made, owned by the same person or subject to an obligation of assignment to the same person.

Claims 1-7 and 13-48 are rejected under 35 U.S.C. § 103 as being unpatentable over Rössling et al. (5,501,863; Protest filed 4/23/99), Tickner '251 (Protest filed 4/23/99), Tickner et al. '885 (C; Protest filed 4/23/99), Albayrak (5,730,954; PTO-892 dated 9/24/99) Glajch et al. (5,147,631; PTO-892 dated 9/24/99), and Hilmann et al. (4,466,442; Protest filed 4/23/99) in view of Lincoff et al. (PTO-892 dated 9/24/99), Lincoff et al. (PTO-892 dated 9/24/99), Gardner et al. (PTO-892 dated 9/24/99) Jacobs (PTO-892 dated 9/24/99) and the Dupont Technical Bulletin (PTO-892 dated 9/24/99)²⁵ for reasons of record stated in the Office Action dated September 29, 1999.

Applicant's arguments filed on March 29, 2000²⁶ have been fully considered but they are not deemed to be persuasive²⁷. Within the response, the Patentee's arguments fall into two groups; 1) lack of *prima facie* case; and 2) evidence of unexpected results to overcome the *prima facie* case. This Office Action follows the same order.

Lack of *prima facie* case

1) Patentee assert that so many references have been used that the number of references alone are an indication of the lack of *prima facie* obviousness; however, it is noted that the reason that there are a number of references cited is actually due to the breadth of Patentee's claims. Unlike the cited case, law the references are

²⁵Patentee's arguments concerning Illum (PTO-892 dated 9/24/99) and Swanson (PTO-892 dated 9/24/99) were considered persuasive. Consequently, they have been withdrawn as references.

²⁶and further amplified in the response to protest filed May 22, 2000. Except for issues raised only in the response to protest, the two responses will be discussed together.

²⁷It is noted that Patentee has frequently availed themselves of the opinions of several prominent practitioners in the diagnostic composition arts. Their opinions have been fully and carefully considered in the course of considering Patentee's arguments. Since these opinions were used primarily to amplify attorney' arguments, they will be discussed in conjunction with said arguments.

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not individually combined but instead are taken in two groups with the first group being held obvious in view of the second group.²⁸

2) Examiner does not concur with Patentee's description of the instant claims. Patentee appears to be asserting limitations which are not present in the claims.²⁹ Patentee asserts that independent claims 1-7, 13-15, 18, 21-26, 32, 35, and 37-42 have one or more thin layers of amphiphilic surfactants which surround the gas bubbles. Patentee is apparently reading this limitation into the term "stabilized"; however, the two terms are not equivalent since at the time of the invention, there were many known techniques for stabilizing microbubbles. In addition, claim 1, for example, merely requires that the microbubbles be surrounded by a evanescent gas/liquid interfacial closed surface. The broadest reasonable meaning of these terms in their ordinary usage³⁰ is simply that the microbubbles are suspended in an aqueous medium. "Evanescent" is defined by Webster³¹ to mean "tending to vanish like vapor; transient". Thus, whatever interface is present is apparently claimed to be transient. Further, Claim 1 does not even require that the microbubbles be "stabilized". Thus, the broadest reasonable meaning of claim 1 does not require that anything be present in the aqueous phase other than ... water.³² Therefore, claim 1 (and many of the other independent claims set forth above as well) are simply drawn to microbubbles of one of the claimed gases suspended in water which may or may not contain additional ingredients.

²⁸Although as is clear from the original rejection (and further discussed below), several of the references render the claim designated inventions *prima facie* obvious by themselves as well as when taken with the ophthalmological references.

²⁹It is noted that throughout Patentee's response, numerous assertions are made both in the body of the response and in the accompanying declarations which tout advantages of Patentee's specific examples and preferred embodiments over compositions which would appear to also fall within the metes and bounds of the instant claim designated invention. Patentee is reminded that such statements create a prosecution history estoppel that could prevent them from enforcing the full scope of their claims (see, for example, *Bayer AG v. Elan Pharmaceuticals*, 54 USPQ 2d, 1710, CA FC 2000).

³⁰see *In re Zletz* and *In re Morris*, cited above.

³¹Webster's Ninth new Collegiate Dictionary. Mirriam-Webster, Inc. USA, 1990

³²but of course does not prohibit any other ingredients whatsoever.

3) Examiner notes the extensive review of the case law concerning obviousness on pages 12-15 of the response; however, since the review does not appear responsive to any specific issues raised in the rejection, it will not be further discussed.

4) Patentee asserts that Rössling et al.'s particles are different than the claim designated invention because the particles taught by Rössling et al. are surrounded by a rigid shell; however, as noted before, Patentee is reading limitations into their claims which are not present. As noted above,³³ claims 1-7, 13-15, 18, 21-26, 32, 35 do not require a substantial membrane; however, other than the term "evanescent", which appears to exclude Patentee's description of their invention since it appears to exclude any form of stable interface, said claims do not specifically exclude a more substantial membrane. As for claims 16, 17, 19, 20, 27-31, 33, 34, and 36-48, they clearly do encompass the shells of Rössling et al. since they specify that the microbubbles are surrounded by a membrane. Certainly, the broadest reasonable meaning of the term "membrane" would also include Rössling et al.'s coatings particularly since the instant specification does include various polymers as potential membrane materials.

5) Patentee asserts that the gas filled spaces of the particles of Rössling et al. are "generally" too small to provide good echogenic response. Since the intended use of the particles of Rössling et al. is as an *in vivo* ultrasonic contrast agent, such an assertion is essentially an allegation that the invention of Rössling et al. does not work i.e. that their claims are not enabled. Since US patents are presumed to be valid and enforceable until proven otherwise,³⁴ a substantial burden is on Patentee to prove the invalidity of the patent.

6) Patentee asserts that Rössling et al. fail to teach the limitation that their contrast agent is resistant to pressure increases which occur upon injection into the blood stream; however, this assertion is clearly incorrect since Rössling et al., in fact, teach (see col. 19, line 51 - col. 20, line 22) that when injected intravenously their

³³point 2 under the § 103 rejection.

³⁴*In re Sasse*, 207 USPQ 107, CCPA 1980; see also MPEP § 2121.02

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contrast agents provide good ultrasonic contrast effects in both ventricles. Moreover, Administrative Notice is taken that one of the primary long felt needs at the time of Patentee's invention was the development of ultrasonic contrast agents which could withstand the substantial pressure changes that occur in the vascular space. Thus, any ultrasonic contrast agent asserted to be intended for vascular use would be fully expected to achieve good contrast in the face of very large pressure changes (on the order of 50-200 mmHg Δ P). Patentee is reminded that the prior art is not required to provide an *ipsi verbis* recitation of the instant claims but instead must teach the elements of the claims.

7) Patentee asserts that Rössling et al. fail to teach all the limitations of all the dependent claims; however, while it is true that Rössling et al. does not teach all the elements of all the claims, Rössling et al. is cited as being combined with multiple references. *In re Keller* states:³⁵

"Test of obviousness is not whether features of secondary references may be bodily incorporated into primary reference's structure, nor whether claimed invention is expressly suggested in any one or all of references; rather, test is what combined teachings of references would have suggested to those of ordinary skill in art."

"One cannot show nonobviousness by attacking references individually where rejections are based on a combination of references"

8) Patentee asserts that Rössling et al. does not teach fluorinated gases as preferred; however:

a) Rössling et al. does teach one of the claim designated fluorinated gases (SF₆) as preferred.³⁶

b) A reference is relied upon for all that it teaches, not just its preferred or exemplified embodiments.³⁷

³⁵208 USPQ 871, CCPA 1981

³⁶see column 3, lines 23-24

³⁷*In re Lamberti*, 192 USPQ 278, CCPA, 1976

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9) Patentee asserts that Rössling et al. fails to provide any teaching or suggestion to combine it with any of the other references used.³⁸ However, as stated in the Office Action mailed September 29, 1999:

While the prior art references fail to particularly teach each and every gas that would be poorly soluble, it would have been obvious to those of ordinary skill in the art that essentially any poorly soluble gas could be used because the prior art references teach that a large and representative list of poorly soluble gases are useful for ultrasonic imaging. One of ordinary skill would have been motivated to particularly select poorly soluble molecules from among the possible gases to be used in each of Rössling et al. Tickner '251, Tickner et al. '885, Glajch et al., Swanson and Albayrak et al. because Lincoff et al., Lincoff et al., Gardner et al. and Jacobs teach the desirability of using poorly soluble gases in *in vivo* ultrasonic applications

Thus, the teaching to combine Rössling et al. with the other references arises from the fact that Rössling et al. teaches that fluorinated gases may be used in their preparation for ultrasound and thus provides a suggestion to determine which fluorinated gases would work best as well as indicating (especially when taken together) that fluorinated/ low solubility gases work in such a wide variety of preparations that one of ordinary skill would readily understand that they in fact would work in essentially any ultrasound contrast preparation.. Consequently, while the various ultrasound references cited are not combined in this rejection in the sense that the teachings of one are being substituted into the teachings of another, they are being taken collectively to show that it was known in this field of endeavor at the time of the invention that fluorinated gases provide a viable alternative to the air that was used previously in essentially any type of gas containing ultrasonic contrast agent that an artisan would care to invent.

10) Patentee asserts that the gelatin included in the invention of Tickner et al. would not function as an amphiphilic surfactant and would not be strongly attracted to the gas liquid interface. However, this assertion is directly contradictory to Tickner et al. which specifically states that the gelatin would act as an amphiphile for the gas bubbles and would form a membrane around them.³⁹ In addition, as noted above, many of the instant claims do not require any particular

³⁸It is noted that this same general statement is asserted for all the cited references. As this response applies equally to all references, it is only being addressed once.

³⁹see col. 3, lines 54 - 65.

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structural layer at the gas/liquid interface and thus would encompass free gas microbubbles.

Moreover, Tickner et al.'s teaching of using gelatin as a suspending agent for the microbubbles until injection whereupon they would be released into the blood would clearly be encompassed within the instant claims description of a transient (evanescent) gas/liquid interface. Certainly, there is no requirement in the instant claims that the stabilizing substance be strongly attracted to the interface.

11) Patentee asserts that Tickner et al. fail to teach that their microbubbles should be resistant to collapse due to pressure changes found in the bloodstream. As noted above for Rössling et al., this assertion is clearly incorrect since Tickner et al., in fact, teach (see example) that when injected intra-arterially their contrast agents provide good ultrasonic contrast effects. Moreover, Administrative Notice is taken that one of the primary long felt needs at the time of Patentee's invention was the development of ultrasonic contrast agents that could withstand the substantial pressure changes which occur in the vascular space. Thus, any ultrasonic contrast agent asserted to be intended for vascular use would be fully expected to achieve good contrast in the face of very large pressure changes (on the order of 50-200 mmHg ΔP).

12) Patentee asserts that Tickner's ('391) particles are different than the claim designated invention because the particles taught by Tickner are surrounded by a rigid shell; however, as noted before, Patentee is reading limitations into their claims which are not present. As noted above,⁴⁰ claims 1-7, 13-15, 18, 21-26, 32, 35 do not require a substantial membrane; however, other than the term "evanescent", which appears to exclude Patentee's description of their invention since it appears to exclude any form of stable interface, said claims do not specifically exclude a more substantial membrane. As for claims 16, 17, 19, 20, 27-31, 33, 34, and 36-48, they clearly do encompass the shells of Tickner since they specify that the microbubbles are surrounded by a membrane. Certainly, the broadest reasonable meaning of the term "membrane" would also include Tickner's coatings particularly

⁴⁰point 2 under the § 103 rejection.

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since the instant specification does include various polymers as potential membrane materials.

13) Patentee asserts that the gas filled spaces of the particles of Tickner '391 are "generally" too small to provide good echogenic response. Since the intended use of the particles of Tickner is as an *in vivo* ultrasonic contrast agent, such an assertion is essentially an allegation that the invention of Tickner et al. does not work i.e. that their claims are not enabled. Since US patents are presumed to be valid and enforceable until proven otherwise,⁴¹ a substantial burden is on Patentee to prove the invalidity of the patent.

14) Patentee asserts that Tickner '391 teaches that their particles may be ground to provide smaller particles while the instant particles would be destroyed by such grinding; however, this argument does not appear to be relevant since:

- a) Patentee's process claims do not exclude additional process steps.
- b) the instant invention to which Patentee is referring is their exemplified invention, not their claimed invention. As noted above, the instant invention is much broader in scope than Patentee appears to recognize.
- c) Tickner does not require that his particles be ground.

15) Patentee asserts that fluorinated gases are not taught by Tickner '391 as preferred; however, as noted above, A reference is relied upon for all that it teaches, not just its preferred or exemplified embodiments.⁴²

16) Patentee asserts that Glajch et al.'s particles are different than the claim designated invention because the particles taught by Glajch et al. are surrounded by a rigid shell; however, as noted before, Patentee is reading limitations into their claims which are not present. As noted above,⁴³ claims 1-7, 13-15, 18, 21-26, 32, 35 do not require a substantial membrane; however, other than the term "evanescent", which appears to exclude Patentee's description of their own invention since it appears to exclude any form of stable interface, said claims do not specifically

⁴¹ *In re Sasse*, 207 USPQ 107, CCPA 1980; see also MPEP § 2121.02

⁴² *In re Lamberti*, 192 USPQ 278, CCPA, 1976

⁴³ point 2 under the § 103 rejection.

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exclude a more substantial membrane. As for claims 16, 17, 19, 20, 27-31, 33, 34, and 36-48, they clearly do encompass the shells of Glajch et al. since they specify that the microbubbles are surrounded by a membrane. Certainly, the broadest reasonable meaning of the term "membrane" would also include Glajch et al.'s membrane materials particularly since the instant specification does include various polymers as potential membrane components.

17) In the same vein, the fact that Glajch et al. teach that their particles may have a non-spherical morphology or that some of the air containing pores are not completely encapsulated does not distinguish Glajch et al. from the instant invention because Patentee's claims do not require that their microbubbles be spherical nor is there any limitation that all pores must be encapsulated. In addition, Glajch et al. teach that at least some of the air containing pores are entirely surrounded by the membrane material⁴⁴ and are spherical in shape.⁴⁵

18) Patentee asserts that Glajch et al. fails to provide evidence that their invention works; however:

a) there is no requirement in US Patent law that a patent contain any specific examples showing specific reduction to practice.

b) Contrary to Patentee's statement, Glajch et al. provides clear evidence that their microballoons do work *in vitro* (as well as exemplifying several specific compositions).

c) A reference is relied upon for all that it teaches, not just its preferred or exemplified embodiments.⁴⁶

19) Patentee asserts that because the particles of Glajch et al. are more rigid, they should not resonate as well as microbubbles with a more fluid membrane; however, mere allegations or even opinions of artisans asserting unexpected results are generally not persuasive. An allegation of unexpected should be supported by data comparing the cited prior art against the claim designated invention in a side-

⁴⁴see column 5, lines 10-22.

⁴⁵see column 5, lines 25-28.

⁴⁶*In re Lamberti*, 192 USPQ 278, CCPA, 1976

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by-side manner.⁴⁷ Further, as noted above, the instant claims actually encompass the particles of Glajch et al. and thus could not be unexpectedly better than them.

20) Patentee asserts that Glajch et al. fail to teach the limitation that their contrast agent is resistant to pressure increases which occur upon injection into the blood stream; however, this assertion is clearly incorrect since Glajch et al., in fact, teach (see col. 3, lines 2-12) that their particles are intended for *in vivo* ultrasonic imaging of the cardiovascular system. Moreover, Administrative Notice is taken that one of the primary long felt needs at the time of Patentee's invention was the development of ultrasonic contrast agents which could withstand the substantial pressure changes that occur in the vascular space. Thus, any ultrasonic contrast agent asserted to be intended for vascular use would be fully expected to achieve good contrast in the face of very large pressure changes (on the order of 50-200 mmHg ΔP). Patentee is reminded that the prior art is not required to provide an *ipsis verbis* recitation of the instant claims but instead must teach the elements of the claims.

21) Patentee asserts that Glajch et al. do not teach or suggest dry precursors of their particles; however, Patentee's attention is drawn to example 3 (among other places) wherein Glajch et al. specifically teach the formation and storage of dry microballoon precursors.

22) Patentee asserts that fluorinated gases are not taught by Glajch et al. as preferred; however, as noted above, a reference is relied upon for all that it teaches, not just its preferred or exemplified embodiments.⁴⁸ Moreover, Glajch et al. specifically teach fluorinated and halogenated hydrocarbon species.

23) Patentee asserts that the microbubbles of Hilmann et al. "have properties very similar to free gas microbubbles and not to the stabilized microbubbles or microballoons of the '774 reissue claims." Patentee sets forth declaration evidence purporting to show this assertion. However, this evidence is not persuasive for the following reasons:

⁴⁷ *In Re Eisenhut*, 114 USPQ 287, CCPA 1957; *Ex parte Raske*, 28 USPQ 2d 1304, BdPatApp & Inter. 1993; *In re Lindner*, 173 USPQ 356, CCPA 1972

⁴⁸ *In re Lamberti*, 192 USPQ 278, CCPA, 1976

a) Since the intended use of the particles of Hilmann et al. is as an *in vivo* ultrasonic contrast agent, such an assertion is essentially an allegation that the invention of Hilmann et al. does not work i.e. that their claims are not enabled. Since US patents are presumed to be valid and enforceable until proven otherwise,⁴⁹ a substantial burden is on Patentee to prove the invalidity of the patent as a whole.

b) the evidence presented does not provide sufficient detail about the procedures used to test example 2. For example, the means by which injection and shaking were accomplished; the time between preparation and analysis; the equipment used to measure contrast were not provided.

c) Patentee only tested one of Hilmann et al.'s 11 examples and failed to state why that one was selected over the others.

d) Patentee teaches that the microbubbles do provide transient contrast; therefore, the microbubbles do function. If Patentee is attempting to show unexpected superiority of their invention over Hilmann et al., then the preparations must be tested in a side by side manner with all variable fixed but one. In the instant case, it is impossible to determine if the preparation conditions, the exact amount of the constituents, the gas used, or one of many other factors led to larger microbubble sizes and less contrast.

e) With the exception of the gas used, Patentee's instant claims encompass the invention of Hilmann et al. and therefore it is unclear how they could be unexpectedly better than them. In particular, the allegation that the microbubbles of Hilmann et al. are more like free gas microbubbles and that the surfactants used by Hilmann et al. are not film forming is particularly puzzling since the surfactants used by Hilmann et al. are specifically taught and exemplified in the instant patent for the formation of the instantly claimed microbubbles and microballoons. Certainly, the use of the same surfactants would be encompassed within the instant claims.

⁴⁹*In re Sasse*, 207 USPQ 107, CCPA 1980; see also MPEP § 2121.02

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24) Patentee asserts that Hilmann et al. fail to teach that their microbubbles should be resistant to collapse due to pressure changes found in the bloodstream. As noted above for both Rössling et al. and Tickner et al., this assertion is clearly incorrect since Hilmann et al., in fact, teach (see example 11) that when injected intravenously their contrast agents provide good ultrasonic contrast effects in the right ventricle of dogs. Moreover, Administrative Notice is taken that one of the primary long felt needs at the time of Patentee's invention was the development of ultrasonic contrast agents that could withstand the substantial pressure changes which occur in the vascular space. Thus, any ultrasonic contrast agent asserted to be intended for vascular use would be fully expected to achieve good contrast in the face of very large pressure changes (on the order of 50-200 mmHg ΔP).

25) Patentee asserts that the clathrates of Albayrak release microbubbles of gas by dissolving rather than being injected as microbubbles. Examiner concurs that the clathrate complexes of Albayrak store the gas in a different manner prior to administration. However, upon mixing the clathrates with an aqueous medium (which is performed prior to *in vivo* administration), they do dissolve releasing microbubbles similar to the claim designated microbubbles. Since the only active step in certain instant claims (such as claim 1) is forming microbubbles and/or microvesicles in the presence of a gas, the step of dissolving clathrates to form microbubbles would be encompassed.

26) Patentee asserts that Albayrak do not teach that their microbubbles would have any type of membrane or interface. However, as noted above, the broadest reasonable meaning of claim 1 (among other claims) does not require that anything be present in the aqueous phase other than ... water.⁵⁰ Therefore, claim 1 (and many of the other independent claims set forth above as well) are simply drawn to microbubbles of one of the claimed gases suspended in water which may or may not contain additional ingredients. Certainly, the microbubbles of Albayrak et al. would be encompassed within this claim.

⁵⁰but of course does not prohibit any other ingredients whatsoever.

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27) Patentee contests that the addition of albumin to the contrast medium would not result in albumin assembling at the air/gas interface but instead suggests that denaturation is required for albumin to become present at the interface. However, while it is possible that a process such as denaturation is necessary to form a substantial tangible membrane of albumin, it is clear that since albumin is an amphiphile, at least some of the albumin present in the solution would tend to assemble at the interface. Again, as noted above, there are certainly no limitations in the instant claims on how much of the amphiphile must be present at the interface. In addition,⁵¹ Albayrak et al. teach that phospholipids (e.g. lecithin) may also be included in the aqueous medium.⁵² Since lecithin is a film-forming surfactant which exists in lamellar or laminar form, it would stabilize the microbubbles of Albayrak et al. in the same manner as that of the claim designated invention.

28) Patentee asserts that Albayrak et al. fail to teach the limitation that their contrast agent is resistant to pressure increases which occur upon injection into the blood stream; however, this assertion is clearly incorrect since Albayrak et al., in fact, teach (see col. 2, lines 55-63) that their particles are intended for *in vivo* ultrasonic imaging of both ventricles of the heart. Moreover, Administrative Notice is taken that one of the primary long felt needs at the time of Patentee's invention was the development of ultrasonic contrast agents that could withstand the substantial pressure changes which occur in the vascular space. Thus, any ultrasonic contrast agent asserted to be intended for vascular use would be fully expected to achieve good contrast in the face of very large pressure changes (on the order of 50-200 mmHg ΔP). Patentee is reminded that the prior art is not required to provide an *ipsi verbi* recitation of the instant claims but instead must teach the elements of the claims.

29) Patentee asserts that Albayrak et al. does not teach any fluorinated gases as preferred; however:

⁵¹as pointed out on page 28 of the protest filed April 14, 2000.

⁵²column 7, lines 16-18.

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a) Albayrak et al. does, in fact, particularly exemplify the use of a fluorinated gas (SF₆).

b) A reference is relied upon for all that it teaches, not just its preferred or exemplified embodiments.⁵³

30) Patentee asserts that Lincoff et al., Lincoff et al., Gardner et al. and Jacobs do not teach using microbubbles for ultrasound. Examiner concurs, but, as stated in the Office Action mailed September 29, 1999:

a) It is the combination of references which must provide a reasonable expectation of success, not one or two references taken from the whole.

b) As succinctly stated in *In re Keller*:⁵⁴

"One cannot show nonobviousness by attacking references individually where rejections are based on a combination of references"

Simply pointing out the fact that these references teach bubbles of a larger size than would be safe for *in vivo* use or that the bubbles were injected into a different space is not pertinent except in the context of whether one of ordinary skill would then have been motivated to combine them with the other prior art.

c) Lincoff et al., Lincoff et al., Gardner et al. and Jacobs are used in the rejection as secondary references and are only used to show that certain specific fluorinated gases have very low solubilities and have been used safely *in vivo*. Thus, questions regarding issues specific to ultrasound imaging, such as bubble size, etc. are not relevant to teachings of these particular references.

31) Patentee asserts that since Lincoff et al., Lincoff et al., Gardner et al. and Jacobs teach that their microbubbles would expand, the artisan in the ultrasonic contrast arts would not look to their perfluorinated gases because the uncontrolled expansion would lead to the risk of emboli. However:

a) Several of the primary references⁵⁵ teach that various types of fluorinated gases may be used for *in vivo* and more specifically, intravascular

⁵³ *In re Lamberti*, 192 USPQ 278, CCPA, 1976

⁵⁴ 208 USPQ 871, CCPA 1981

⁵⁵ Rössling et al., Tickner, and Tickner et al.

ultrasonic imaging. Thus, the question of safety and stability is already answered by these primary references. In addition, Administrative notice is taken that one of ordinary skill would be well aware that as the size of (micro)bubbles increase, their *in vivo* longevity increases as well. Consequently, one of ordinary skill would understand that decreasing the volume of the bubbles by several orders of magnitude would also dramatically decrease the duration of the microbubbles. Of course, the exact correlation between size and duration would not be absolutely predictable; however, it would merely be a matter of routine experimentation to determine the exact relationship at micron size.

b) In addition, Lincoff et al.⁵⁶ state the following:

"Animal experiments that measure the expansion of these gases revealed that with remarkable uniformity CF_4 expands 1.9 times, C_2F_6 3.3 times, C_3F_8 4 times and C_4F_{10} 5 times."

Therefore, it can be seen that at the time of the publication of the Lincoff et al. reference, not only was it known (as Patentee stated) that when perfluorocarbons are administered *in vivo*, they expand, but it was also known exactly how much expansion occurred for each gas. Thus, expansion was a well characterized phenomenon which could easily be accounted for⁵⁷ when using the desired perfluorocarbons. Consequently, what Lincoff et al., Lincoff et al., Gardner et al. and Jacobs would actually convey to the ordinary artisan is that:

- i) perfluorocarbons are very insoluble *in vivo*.
- ii) perfluorocarbons will persist *in vivo* for very long periods of time.
- iii) they expand in a well characterized way which should be taken into account when determining the amount to be administered.
- iv) they are safe in much higher quantities than that used in ultrasound.

⁵⁶*ibid.*, page 547

⁵⁷as Lincoff et al. did in the eye by adjusting the amount of gas administered to produce the desired final amount of gas.

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Consequently, Lincoff et al., Lincoff et al., Gardner et al. and Jacobs provided a clear solution to several problems which artisans in the ultrasonic field were grappling with as evidenced by their own disclosures.

32) The Patentee asserts that Lincoff et al., Lincoff et al., Gardner et al. and Jacobs are neither in the same field of endeavor as the primary ultrasound references nor are they reasonably pertinent to the problem the patentee was concerned with. In making these assertions, Patentee is apparently setting forth the basis for asserting that these references are non-analogous art.

As alleged by the Patentee, a reference must be from an analogous art. *In re Oetiker*⁵⁸ provides excellent guidance on the test for determining when prior art is analogous:

"In order to rely on a reference as a basis for rejection of the Patentee's invention, the reference must either be in the field of the Patentee's endeavor, or, if not, then be reasonably pertinent to the particular problem with which the inventor was concerned. Patent examination is necessarily conducted by hindsight, with complete knowledge of the Patentee's invention, and the courts have recognized the subjective aspects of determining whether an inventor would reasonably be motivated to go to the field in which the examiner found the reference, in order to solve the problem confronting the inventor. We have reminded ourselves and the PTO that it is necessary to consider the "reality of the circumstances" - in other words, common sense - in deciding in which fields a person of ordinary skill would reasonably be expected to look for a solution to the problem facing the inventor."

As explained in the Office Action mailed September 29, 1999, Lincoff et al., Lincoff et al., Gardner et al. and Jacobs are not in the same field of endeavor as Patentee's invention. Thus, Examiner concurs with Patentee that said references are not in the same technical field. However, (also in the Office Action mailed September 29, 1999), a detailed analysis was given as to why said references were reasonably pertinent to the particular problem with which the inventor was concerned, as reproduced below:

While the Lincoff et al. publications and Gardner et al. are not directed towards ultrasonic imaging and thus could not be considered to be within the same field of endeavor as the references cited above, they specifically address the importance and the usefulness of small perfluorocarbon gases *in vivo*; giving particular attention to the long persistence of their effect due to their insolubility. Thus, they are pertinent to the problem that inventors in the ultrasonic imaging arts were trying to solve at the time of the invention. Tickner et al. (col. 4, lines 16-29) and Rössling et al. specifically address the importance of finding a gas which has a long duration in the blood and note low

solubility as a criteria. In addition, Jacobs serves as a bridge between the ultrasonic imaging arts and the therapeutic art in that Jacobs also is primarily concerned with the therapeutic uses of the perfluorocarbon gases yet also teaches that ultrasonic imaging techniques may be applied to bubbles of perfluorocarbon gases. While the type of large bubble ultrasonic imaging used by Jacobs is not the same as microbubble imaging, it still serves as a bridge in that a person of ordinary skill, while searching through the ultrasonic imaging literature, would find a cross reference to Jacobs and thus find further information about the duration problem they were attempting to solve. It is also important to note that Lincoff et al., Lincoff et al., Gardner et al. and Jacobs teach that small fluorinated molecules are safe in quantities that are orders of magnitude beyond the quantities injected in a bolus of microbubbles. This is also a problem that would be extremely pertinent when determining what gas to use in *in vivo* ultrasonic imaging.

Thus, the Office Action set forth a *prima facie* basis as to why Lincoff et al., Lincoff et al., Gardner et al. and Jacobs were reasonably pertinent to the particular problem with which the inventor was concerned, i.e. finding a gas preparation that persists for a long time *in vivo*. The blanket statement by Patentee that the benefits extolled by said references were antithetical to those faced by those who were developing ultrasound contrast agents at the time, simply because of the expansion properties of the microbubbles, is not considered persuasive; particularly since the characteristics of the expansion were well characterized (and thus fully predictable) as noted above. In addition, Patentee has omitted what Lincoff et al. considered the primary benefit of the perfluorinated gases. Lincoff et al.⁵⁹ states at pages 546-547, their primary advantage:

"In 1977, the Cornell group began a search for a gas with a longer staying potential than either SF₆ or C₄F₈. Theoretically an ideal gas for a tamponade should maintain a therapeutic volume for a least 8 to 11 days, the time that it takes for retinal adhesion to become maximum. ... The quality that makes the perfluorocarbons long staying in the eye is their insolubility, for gases must get into solution in order to cross the blood aqueous barrier and escape the eye. A secondary effect of insolubility is expansion. Because the blood gases are more soluble than the perfluorocarbons, they diffuse more rapidly across the blood aqueous barrier and expand the intraocular perfluorocarbon bubble."

Thus, it is clear that Lincoff et al appreciated that the insolubility of the perfluorocarbon gases is their primary advantage for *in vivo* use. Such a benefit is not "antithetical" to providing a safe and size stable *in vivo* agent but instead provides motivation to look to the perfluorinated compounds taught in their papers as ultrasonic contrast agents.

In addition, Patentee is reminded that the secondary ophthalmological references are combined with the primary references so as to show that one of

⁵⁹ *Ophthalmology* 90:546-551 (1983)

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ordinary skill in the art would have found it obvious to look to specific perfluorocarbon gases within the broader genera (e.g. Freons and halogenated gases) taught by the primary references. However, Patentee's claim designated species are encompassed with in the prior art recitations of the primary references and, as such, are rendered obvious by them without the necessity of including the secondary references.⁶⁰

33) Patentee asserts that Jacobs could not serve as a bridge because it is also in the field of ocular surgery; however, the only point that Examiner was attempting to make⁶¹ was that ultrasonic imaging had been used in conjunction with these specific perfluorocarbon gases and that if one of ordinary skill in the ultrasonic imaging art were doing an electronic or classification search on ultrasonic imaging, then this reference would lead them to the use of these gases *in vivo* and would call their *in vivo* stability and low solubility to the artisan's attention.

34) Patentee asserts that the Dupont Technical bulletin does not teach microbubbles; however, the bulletin (as noted in the Office Action mailed September 29, 1999) was included simply to show that at least some the claim designated fluorocarbons are well known Freons®.

35) Patentee (on pages 39-43 of the response) asserts a lack of motivation to combine the references and then recapitulates the supposed deficiencies of each reference. Since the individual references are discussed in detail above, they will not be discussed again.

36) Finally, Patentee asserts that the references were combined using impermissible hindsight; however, Patentee is reminded that:

"Any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning, but so long as it takes into account only knowledge which was within level of ordinary skill at time claimed invention was made and does not include knowledge gleaned only from Patentee's disclosure, reconstruction is proper."⁶²

⁶⁰For example, the inclusion of Freon® in Tickner et al. is, of course, the same scope as those instant claims which are also directed to Freons® and thus also encompasses most halogenated hydrocarbons.

⁶¹i.e. when referring to Jacobs as a bridge. Obviously, the discussion set forth above regarding analogous art applies equally to Jacobs.

⁶²*In re McLaughlin*, 170 USPQ 209, CCPA 1971

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As stated in the Office Action dated September 29, 1999 and further discussed above, Examiner believes there was sufficient motivation in the primary references to look to other places for specific fluorinated gases which would solve the problems which artisans in the ultrasonic imaging arts were attempting to solve.

Secondary Considerations

Patentee has provided a declaration from Dr. Schneider⁶³ which provides a showing of unexpected results for the claim designated invention. The following defects were found in the declaration:

1) The declaration is not commensurate in scope with the entire claim designated invention.⁶⁴ Claims 1 and 16 being representative. They are directed to a method of preparing an ultrasonic imaging agent using any one of eleven fluorinated gases and surrounded by essentially any type of boundary material.⁶⁵ Only one sample was tested. To be commensurate in scope, Patentee would need to test unsaturated, partially fluorinated⁶⁶ and cyclic gases as well. One of ordinary skill would expect that permutations such as unsaturation, ring structures and the presence of chlorine and bromine atoms in the gas would have a major impact on the persistence of the microbubbles but would not be able to quantify the persistence difference to determine if the persistence of the other gases was also unexpected over the prior art gases. In addition, in statements made in the response to the protest filed May 22, 2000, Patentee clearly appreciated the importance of the constituents of the interfacial boundary in the overall persistence and performance of the microbubbles in ultrasonic imaging. Consequently, the declaration is not inclusive of and thus not persuasive for the untested compounds.

⁶³in particular, pages 1-6 of the Schneider declaration filed March 29, 2000.

⁶⁴In re Lindner, 173 USPQ 356, CCPA 1972 provides a discussion of the importance that the testing must be commensurate in scope to the breadth of the protection being sought.

⁶⁵as noted above in the section titled "Lack of *Prima Facie* Case" under point 2

⁶⁶especially in light of the chlorinated and brominated gases claimed.

2) Patentee did not compare the closest prior art. The two closest prior art gases would be sulfur hexafluoride and hexafluoroethane. Of course sulfur hexafluoride and hexafluoroethane are both explicitly claimed in the instant invention. Consequently, any declaration purporting to show unexpected results over these gases cannot be persuasive for claims which include these gases. Moreover, most of the dependent claims, while more limited than claims 1 and 16 would still encompass the prior art gases being tested since most of the dependent claims encompass the entire genera of claim designated gas species.

3) The preparation procedures for the prior art vs. the instant preparations were not side-by-side. Apparently, no attempt was made to control for unfixed variables whatsoever. *In re Dunn* provides guidance:⁶⁷

"We do not feel it an unreasonable burden on the appellant(s) to require comparative examples relied on for non-obviousness to be truly comparative. The cause and effect sought to be proven is lost here in the welter of unfixed variables."

As in *Dunn*, the welter of unfixed variables precludes any clear interpretation of the results.

4) How the *in vivo* tests were conducted and how the quality of ultrasonic images was determined was not indicated. Certainly, there did not appear to be any attempt to apply normal analytical and experimental methods in the testing.⁶⁸

5) The data was not subjected to any type of statistical analysis and it appears that only one test was done for each sample. Proper scientific method requires multiple measurements, so that the data can be averaged and statistical analysis can be performed. Without statistical analysis of the data, it is very difficult to determine the significance, and thus, the "unexpectedness" of the data.

6) Patentee did not test a preparation that was taught in their original specification but instead tested a brand new preparation.

67146 USPQ 479, CCPA, 1965.

68i.e. double blind examination of the images; use of control animals; normalization of animal preparations and quantities of contrast agent and adjuvants used, etc.

7) In light of the deficiencies cited above, the declaration of unexpected results provided is not persuasive of the unobviousness of the claim designated invention.

8) Patentee has asserted that there has been a long felt need for their invention and has further asserted that others have tried and failed to address this need. To support their position, they have brought forward a declaration by Dr. Wheatley that is purported to show the existence of a long felt need that has not been met by others.

To establish a long felt need first requires objective evidence that the need has been a persistent one that was recognized by those of ordinary skill in the art.⁶⁹ In the instant case, Patentee has clearly established such a need existed through the declaration. Second, the long-felt need must not have been satisfied by another before the invention by Patentee.⁷⁰ Patentee asserts that despite the long felt need, no contrast agent has been introduced yet which allows for effective imaging of myocardial perfusion; however, as Patentee is no doubt well aware, there is usually a very long hiatus between the time a pharmaceutical invention is reduced to practice and the time it is brought to market.⁷¹ As Patentee is also aware there are actually at least four other similar commercial products, based upon inventions conceived in the same time period as Patentee's invention. Thus, said other commercial products, if they were invented before Patentee's invention, would actually be the invention which met the long felt need. Since the Patentee is currently involved in both an intra-PTO interference proceeding and other litigation outside the PTO, it is clear that there is some question as to who really met the long felt need first. In addition, there does not appear to be any legal requirement that the person(s) who solved the long felt need brought a commercial product to market. Thus, while the Examiner is not aware if any commercial products are being approved based upon either Rössling et al. or Glajch et al., there are still

⁶⁹ *In re Gershon* 152 USPQ 602, CCPA 1967; *Orthopedic Equipment Co. v. All Orthopedic Devices* 217 USPQ 1281, CA FC 1983

⁷⁰ *Newell V. Kenny* 9 USPQ2d 1417, CA FC 1988.

⁷¹ frequently due to the time required for regulatory approval in both the USPTO and the FDA.

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examples of compositions within their specification which are purported to be useful for myocardial imaging and would thus would have solved the long felt need prior to Patentee. Consequently, it does not appear likely that Patentee's invention has solved a long-felt need.

For the above stated reasons, said claims are properly rejected under 35 U.S.C. § 103. Therefore, the rejection is adhered to.

Protest

The protest filed April 14, 2000 addressed three major issues:

- 1) The error asserted by Patentee is not a correctable one under 35 USC § 251;
- 2) The instant claim designated invention is not entitled to the priority date now claimed by Patentee; and
- 3) The instant claims are rejectable under 35 USC § 102 and § 103 over various references.

Patentee has provided a rebuttal to the issues raised by Protestor in the response filed on May 22, 2000

The arguments set forth by protestor to points 2 and 3 above were fully considered and were incorporated and/or discussed in the sections of this Office Action which dealt with those issues.⁷²

With regards to point 1, Examiner concurs with the arguments and the accompanying case law set forth by Patentee in the Response to Protest. Namely, there appears to be ample precedent that an inadvertent error in claiming priority is correctable under 35 USC § 251.

⁷²Specifically, point 2 was discussed in the section titled "Effective Priority Date" and point 3 was discussed in the sections titled "102 Rejection" and "103 Rejection".

Conclusion

In view of the objections /rejections to the pending claims set forth above, no claims may be allowed at this time.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 CFR 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to the Group 1600 fax machine at 703/308-4556. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30; November 15 1989.

Any inquiry concerning this Office Action or any earlier Office Actions in this application should be directed to Dr. Gary E. Hollinden whose telephone number is 703/308-4521. Dr. Hollinden's office hours are from 6:30 am to 3:00 pm on Monday through Friday.

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Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is 703/308-1285.



Gary E. Hollinden, Ph.D.
Primary Examiner
Group 1600